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Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

19 MAY 2004

The Patent Office
Cardiff Road
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1.	Your reference	MG/PB60402P1
2.	Patent application number *(The Patent Office will fill in his part)*	0411167.0
3.	Full name, address and postcode of the or of each applicant *(underline all surnames)* Patents ADP number *(if you know it)* If the applicant is a corporate body, give the country/state of its corporation.	Glaxo Group Limited Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 0NN, Great Britain 00473587003 United Kingdom
4.	Title of the invention	Novel compounds
5.	Name of your agent *(if you have one)* "Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)* 08072555006 Patents ADP number *(if you know it)*	Corporate Intellectual Property GlaxoSmithKline Corporate Intellectual Property (CN9 25.1) 980 Great West Road BRENTFORD Middlesex TW8 9GS
6.	Priority: Complete this section if you are declaring priority from one or more earlier patent applications, filed in the last 12 months	Country / Priority application number *(if you know it)* / Date of filing *(day / month / year)*
7.	Divisionals: etc Complete this section only if this application is a divisional application or resulted from an entitlement dispute (see note f)	Number of earlier application / Date of filing *(day / month / year)*
8.	Is a Patents Form 7/77 (Statement of inventorship and of right to grant of a patent) required in support of this request?	Yes

Answer YES if:

a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is not named as an applicant, or
c) any named applicant is a corporate body
Otherwise answer NO See note (d)

Patents Form 1/77

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Continuation sheets of this form	0	
Description	30	32
Claim(s)	2	
Abstract	0	
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Priority Documents

Translations of priority documents

Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*

Request for preliminary examination and search *(Patents Form 9/77)*

Request for substantive examination *(Patents Form 10/77)*

Any other documents *(please specify)*

11. **I/We request the grant of a patent on the basis of this application**

Signature(s) ____________ **Date:** 19-May-04

M Gibson

12. Name and daytime telephone number of person to contact in the United Kingdom — M Gibson 01279 644841

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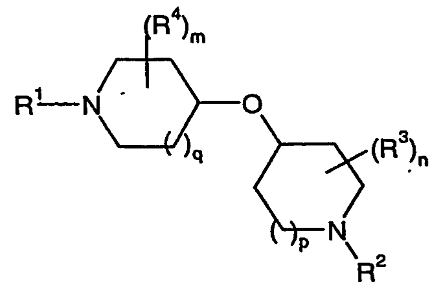
NOVEL COMPOUNDS

The present invention relates to novel piperidine ether derivatives having pharmacological activity, processes for their preparation, to compositions containing them and to their use in the treatment of neurological and psychiatric disorders.

WO 03/24450 (Eisai Co. Ltd) describes a series of heterocyclic cholinesterase inhibitors which are claimed to be useful in the treatment of prion diseases. WO 03/24456 (Eisai Co. Ltd) describes a series of heterocyclic cholinesterase inhibitors which are claimed to be useful in the treatment and prevention of migraine. WO 99/37304 (Rhone-Poulenc Rorer Pharmaceuticals Inc) and WO 01/07436 (Aventis Pharmaceuticals Products Inc) both describe a series of substituted oxoazaheterocyclyl Factor Xa inhibitors. WO 03/103669 and WO 03/088967 (both Schering Corp) describe a series of piperidinyl benzimidazolone compounds as histamine H3 antagonists. WO 02/32893 and WO 02/72570 (both Schering Corp) describe a series of non-imidazole compounds as histamine H3 antagonists.

The histamine H3 receptor is predominantly expressed in the mammalian central nervous system (CNS), with minimal expression in peripheral tissues except on some sympathetic nerves (Leurs *et al.*, (1998), Trends Pharmacol. Sci. **19**, 177-183). Activation of H3 receptors by selective agonists or histamine results in the inhibition of neurotransmitter release from a variety of different nerve populations, including histaminergic and cholinergic neurons (Schlicker *et al.*, (1994), Fundam. Clin. Pharmacol. **8**, 128-137). Additionally, *in vitro* and *in vivo* studies have shown that H3 antagonists can facilitate neurotransmitter release in brain areas such as the cerebral cortex and hippocampus, relevant to cognition (Onodera *et al.*, (1998), In: The Histamine H3 receptor, ed Leurs and Timmerman, pp255-267, Elsevier Science B.V.). Moreover, a number of reports in the literature have demonstrated the cognitive enhancing properties of H3 antagonists (e.g. thioperamide, clobenpropit, ciproxifan and GT-2331) in rodent models including the five choice task, object recognition, elevated plus maze, acquisition of novel task and passive avoidance (Giovanni *et al.*, (1999), Behav. Brain Res. **104**, 147-155). These data suggest that novel H3 antagonists such as the current series could be useful for the treatment of cognitive impairments in diseases such as Alzheimer's disease and related neurodegenerative disorders.

The present invention provides, in a first aspect, a compound of formula (I) or a pharmaceutically acceptable salt thereof:



(I)

wherein:

R^1 represents aryl, heteroaryl,-aryl-X-aryl, -aryl-X-heteroaryl, -aryl-X-heterocyclyl, -heteroaryl-X-heteroaryl, -heteroaryl-X-aryl or –heteroaryl-X-heterocyclyl;
wherein said aryl, heteroaryl and heterocyclyl groups of R^1 may be optionally substituted by one or more (eg. 1, 2 or 3) substituents which may be the same or different, and which are selected from the group consisting of halogen, hydroxy, cyano, nitro, oxo, haloC_{1-6} alkyl, polyhaloC_{1-6} alkyl, haloC_{1-6} alkoxy, polyhaloC_{1-6} alkoxy, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkoxyC_{1-6} alkyl, C_{3-7} cycloalkylC_{1-6} alkoxy, C_{1-6} alkanoyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylsulfonyl, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyloxy, C_{1-6} alkylsulfonylC_{1-6} alkyl, C_{1-6} alkylsulfonamidoC_{1-6} alkyl, C_{1-6} alkylamidoC_{1-6} alkyl, aryl, arylsulfonyl, arylsulfonyloxy, aryloxy, arylsulfonamido, arylcarboxamido, aroyl, or a group $NR^{15}R^{16}$, $-CONR^{15}R^{16}$, $-NR^{15}COR^{16}$, $-NR^{15}SO_2R^{16}$ or $-SO_2NR^{15}R^{16}$, wherein R^{15} and R^{16} independently represent hydrogen, C_{1-6} alkyl or C_{3-6} cycloalkyl or together form a heterocyclic ring;

X represents a bond, O, CO, SO_2, OCH_2 or CH_2O;

R^2 represents C_{3-8} alkyl, C_{3-6} alkenyl, C_{3-6} alkynyl, C_{3-6} cycloalkyl, C_{5-6} cycloalkenyl or $-C_{1-4}$alkyl-C_{3-6} cycloalkyl;
wherein said C_{3-6} cycloalkyl groups of R^2 may be optionally substituted by one or more (eg. 1, 2 or 3) substituents which may be the same or different, and which are selected from the group consisting of halogen, C_{1-4} alkyl or trifluoromethyl groups;

each R^3 and R^4 group independently represents C_{1-4} alkyl;

m and n independently represents 0, 1 or 2;

p and q independently represents 1 or 2;

or a pharmaceutically acceptable salt thereof.

Specific compounds of formula (I) which may be mentioned are those wherein said aryl, heteroaryl and heterocyclyl groups of R^1 may be optionally substituted by one or more (eg. 1, 2 or 3) substituents which may be the same or different, and which are selected from the group consisting of halogen, hydroxy, cyano, nitro, oxo, haloC_{1-6} alkyl, polyhaloC_{1-6} alkyl, haloC_{1-6} alkoxy, polyhaloC_{1-6} alkoxy, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkoxyC_{1-6} alkyl, C_{3-7} cycloalkylC_{1-6} alkoxy, C_{1-6} alkanoyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylsulfonyl, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyloxy, C_{1-6} alkylsulfonylC_{1-6} alkyl, C_{1-6} alkylsulfonamidoC_{1-6} alkyl, C_{1-6} alkylamidoC_{1-6} alkyl, arylsulfonyl, arylsulfonyloxy, aryloxy, arylsulfonamido, arylcarboxamido, aroyl, or a group

$NR^{15}R^{16}$, $-CONR^{15}R^{16}$, $-NR^{15}COR^{16}$, $-NR^{15}SO_2R^{16}$ or $-SO_2NR^{15}R^{16}$, wherein R^{15} and R^{16} independently represent hydrogen, C_{1-6} alkyl or together form a heterocyclic ring.

Alkyl groups, whether alone or as part of another group, may be straight chain or branched and the groups alkoxy and alkanoyl shall be interpreted similarly. The term 'halogen' is used herein to describe, unless otherwise stated, a group selected from fluorine, chlorine, bromine or iodine and the term 'polyhalo' is used herein to refer to a moiety containing more than one (eg. 2-5) of said halogen atoms.

The term "aryl" includes single and fused rings wherein at least one ring is aromatic, for example, phenyl, naphthyl and tetrahydronaphthalenyl.

The term "heterocyclyl" is intended to mean a 4-7 membered monocyclic saturated or partially unsaturated aliphatic ring or a 4-7 membered saturated or partially unsaturated aliphatic ring fused to a benzene ring containing 1 to 3 heteroatoms selected from oxygen, nitrogen or sulphur. Suitable examples of such monocyclic rings include pyrrolidinyl, azetidinyl, piperidinyl, piperazinyl, morpholinyl, tetrahydrofuranyl, tetrahydropyranyl, diazepanyl and azepanyl. Suitable examples of benzofused heterocyclic rings include indolinyl, isoindolinyl, 2,3,4,5-tetrahydro-1*H*-3-benzazepine or tetrahydroisoquinolinyl.

The term "heteroaryl" is intended to mean a 5-6 membered monocyclic aromatic or a fused 8-10 membered bicyclic aromatic ring containing 1 to 3 heteroatoms selected from oxygen, nitrogen and sulphur. Suitable examples of such monocyclic aromatic rings include thienyl, furyl, pyrrolyl, triazolyl, imidazolyl, oxazolyl, thiazolyl, oxadiazolyl, isothiazolyl, isoxazolyl, thiadiazolyl, pyrazolyl, pyrimidyl, pyridazinyl, pyrazinyl and pyridyl. Suitable examples of such fused aromatic rings include benzofused aromatic rings such as quinolinyl, isoquinolinyl, quinazolinyl, quinoxalinyl, cinnolinyl, naphthyridinyl, indolyl, indazolyl, pyrrolopyridinyl, benzofuranyl, benzothienyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzothiazolyl, benzisothiazolyl, benzoxadiazolyl, benzothiadiazolyl and the like.

Preferably, R^1 represents

-aryl (eg. phenyl) optionally substituted by a cyano, $-CONR^{15}R^{16}$ group (eg. $-CON(H)(Me)$ or $-CONMe_2$) or C_{1-6} alkanoyl eg. $-COMe$) group;

-heteroaryl (eg. pyridyl) optionally substituted by a cyano (eg. 5-cyano-2-pyridyl or 6-cyano-3-pyridyl), polyhaloC_{1-6} alkyl (eg. $-CF_3$) or $-CONR^{15}R^{16}$ group (eg. $-CON(H)(Me)$, $-CONMe_2$, $-CON(H)(Et)$, $-CON(H)(Pr)$ or $-CON(H)$(cyclopentyl));

-aryl-X-heterocyclyl (eg. –phenyl-CO-morpholinyl, -phenyl-CO-piperidinyl or –phenyl-CO-pyrrolidinyl);

aryl-X-heteroaryl (eg. –phenyl-oxazolyl or –phenyl-oxadiazolyl) optionally substituted by a C_{1-6} alkyl (eg. methyl) or aryl (eg. phenyl); or

-heteroaryl-X-heterocyclyl (eg. –pyridyl-CO-pyrrolidinyl, -pyridyl-CO-piperidinyl or –pyridyl-CO-morpholinyl).

More preferably, R^1 represents

-heteroaryl (eg. pyridyl) optionally substituted by a cyano (eg. 5-cyano-2-pyridyl or 6-cyano-3-pyridyl), polyhaloC_{1-6} alkyl (eg. $-CF_3$) or $-CONR^{15}R^{16}$ group (eg. –CON(H)(Me), $-CONMe_2$, -CON(H)(Et), -CON(H)(Pr) or –CON(H)(cyclopentyl); or

aryl-X-heteroaryl (eg. –phenyl-oxazolyl or –phenyl-oxadiazolyl) optionally substituted by a C_{1-6} alkyl (eg. methyl) or aryl (eg. phenyl).

Most preferably, R^1 represents pyridyl optionally substituted by a $-CONR^{15}R^{16}$ group (eg. –CON(H)(Me)) or –phenyl-oxadiazolyl optionally substituted by a C_{1-6} alkyl (eg. methyl) group (eg. 3-methyl-1,2,4-oxadiazol-5-yl).

Preferably, m and n represent 0.

Preferably, p and q represent 1.

Preferably, R^2 represents C_{3-8} alkyl (eg. isopropyl), or C_{3-6} cycloalkyl (eg cyclobutyl), more preferably R^2 represents C_{3-6} cycloalkyl (eg cyclobutyl).

Preferred compounds according to the invention include examples E1-E49 as shown below, or a pharmaceutically acceptable salt thereof.

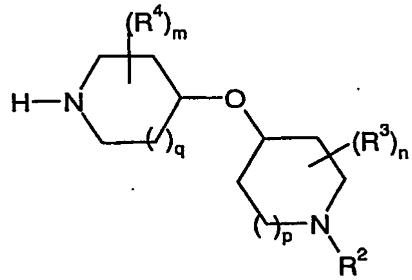
Most preferred compounds according to the invention include: 1-(1-Methylethyl)-4-({1-[4-(3-methyl-1,2,4-oxadiazol-5-yl)phenyl]-4-piperidinyl}oxy)piperidine (E17) and 5-{4-[(1-Cyclobutyl-4-piperidinyl)oxy]-1-piperidinyl}-*N*-methyl-2-pyridinecarboxamide (E38) or a pharmaceutically acceptable salt thereof.

Compounds of formula (I) may form acid addition salts with acids, such as conventional pharmaceutically acceptable acids, for example maleic, hydrochloric, hydrobromic, phosphoric, acetic, fumaric, salicylic, sulphate, citric, lactic, mandelic, tartaric and methanesulphonic.

Certain compounds of formula (I) are capable of existing in stereoisomeric forms. It will be understood that the invention encompasses all geometric and optical isomers of these compounds and the mixtures thereof including racemates. Tautomers also form an aspect of the invention.

The present invention also provides a process for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt thereof, which process comprises:

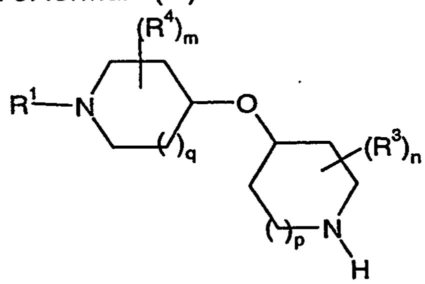
(a) reacting a compound of formula (II)



(II)

wherein R^2, R^3, R^4, m, n, p and q are as defined above, with a compound of formula R^1-L^1, wherein R^1 is as defined above and L^1 represents a suitable leaving group, such as a halogen atom (eg. fluorine or chlorine); or

(b) reacting a compound of formula (III)

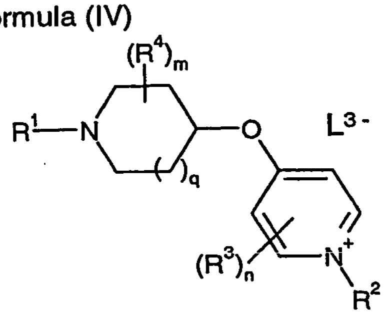


(III)

wherein R^1, R^3, R^4, m, n, p and q are as defined above, with a compound of formula R^2-L^2 where R^2 is as defined above and L^2 represents a suitable leaving group, such as a halogen atom; or

(c) reacting a compound of formula (III) as defined above with a compound of formula R^2=O, wherein R^2 is as defined above; or

(d) preparing a compound of formula (I) wherein p represents 1 which comprises reduction of a compound of formula (IV)



(IV)

wherein R^1, R^2, R^3, R^4 , m, n and q are as defined above and L^3 represents a suitable leaving group such as a halogen atom; or

(e) deprotecting a compound of formula (I) or converting groups which are protected; and optionally thereafter

(f) interconversion to other compounds of formula (I).

Process (a) typically comprises the use of a suitable base, such as potassium carbonate in a suitable solvent such as dimethylsulfoxide or N,N-dimethylformamide at elevated temperature.

Process (b) typically comprises the use of a suitable base such as potassium carbonate in a solvent such as N,N-dimethylformamide.

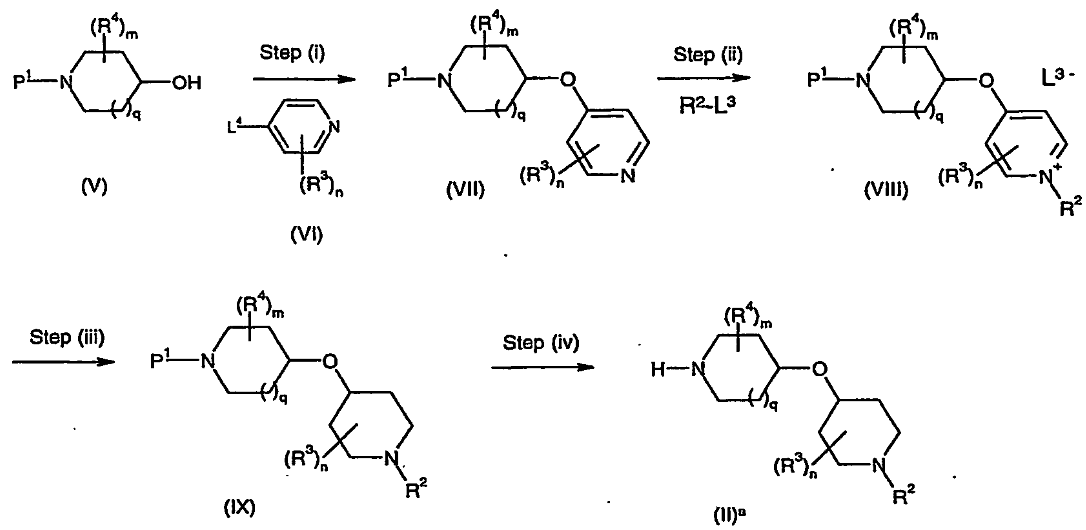
Process (c) typically comprises the use of standard reductive amination conditions with a reducing agent such as sodium triacetoxy borohydride in a suitable solvent such as dichloromethane.

Process (d) is typically carried out under suitable reductive conditions eg using lithium borohydride in combination with ammonium formate and a palladium catalyst in a solvent such as methanol.

In process (e), examples of protecting groups and the means for their removal can be found in T. W. Greene 'Protective Groups in Organic Synthesis' (J. Wiley and Sons, 1991). Suitable amine protecting groups include sulphonyl (e.g. tosyl), acyl (e.g. acetyl, 2',2',2'-trichloroethoxycarbonyl, benzyloxycarbonyl or t-butoxycarbonyl) and arylalkyl (e.g. benzyl), which may be removed by hydrolysis (e.g. using an acid such as hydrochloric acid) or reductively (e.g. hydrogenolysis of a benzyl group or reductive removal of a 2',2',2'-trichloroethoxycarbonyl group using zinc in acetic acid) as appropriate. Other suitable amine protecting groups include trifluoroacetyl ($-COCF_3$) which may be removed by base catalysed hydrolysis or a solid phase resin bound benzyl group, such as a Merrifield resin bound 2,6-dimethoxybenzyl group (Ellman linker), which may be removed by acid catalysed hydrolysis, for example with trifluoroacetic acid.

Process (f) may be performed using conventional interconversion procedures such as epimerisation, oxidation, reduction, alkylation, nucleophilic or electrophilic aromatic substitution, ester hydrolysis or amide bond formation.

Compounds of formula (II) wherein p represents 1 may be prepared in accordance with the following procedure:



wherein R^2, R^3, R^4 , m, n and q are as defined above, L^3 and L^4 represent suitable leaving groups such as a halogen atom, and P^1 represents a suitable protecting group such as t-butoxycarbonyl.

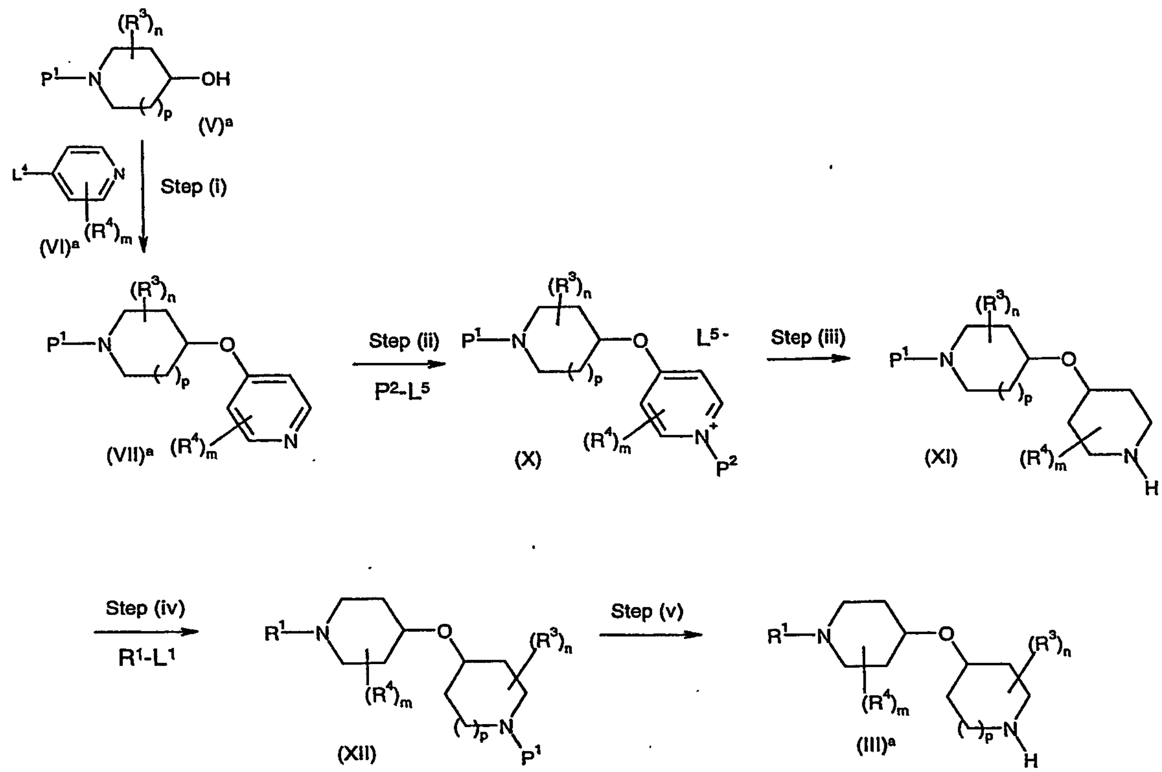
When L^4 represents a suitable leaving group such as a halogen atom (eg. chlorine), step (i) typically comprises the use of a suitable base such as potassium carbonate or sodium hydride in a solvent such as dimethylsulfoxide optionally at elevated temperature.

When L^3 represents a suitable leaving group such as a halogen atom (eg. bromine, iodine), step (ii) is typically carried out in a suitable solvent such as dichloromethane optionally at elevated temperature.

Step (iii) is carried out under reductive conditions eg using lithium borohydride in combination with ammonium formate and a palladium catalyst in a solvent such as methanol.

Step (iv) is a deprotection reaction where the conditions are dependent upon the nature of the group P^1. Removal of a P^1 tert-butoxycarbonyl group can be performed under acidic conditions eg using trifluoroacetic acid in a suitable solvent such as ethyl acetate.

Compounds of formula (III) wherein q represents 1 may be prepared in accordance with the following procedure:



wherein R^1, R^3, R^4, m, n, p, L^1 and L^4 are as defined above, L^5 represents a suitable leaving group such as a halogen atom, P^1 represents a suitable protecting group such as t-butoxycarbonyl and P^2 represents a suitable protecting group such as benzyl

When L^4 represents a suitable leaving group such as a halogen atom (eg. chlorine), step (i) typically comprises the use of a suitable base such as potassium carbonate or sodium hydride in a solvent such as dimethylsulfoxide optionally at elevated temperature.

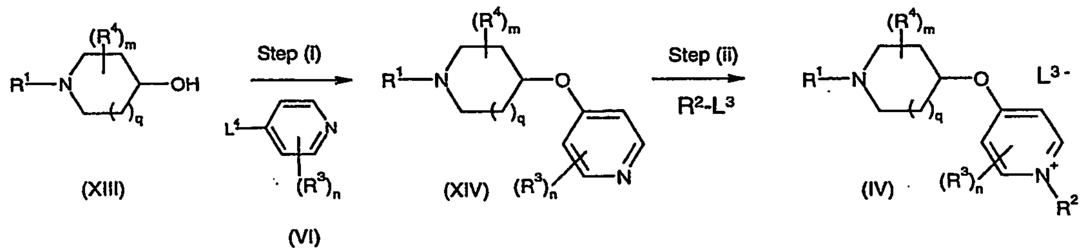
When L^5 represents a suitable leaving group such as a halogen atom (eg. bromine), step (ii) is typically carried out in a solvent such as dichloromethane optionally at elevated temperature.

Step (iii) is carried out under reductive conditions eg using lithium borohydride in combination with ammonium formate and a palladium catalyst in a solvent such as methanol, followed by hydrogenation in the presence of a suitable catalyst such as palladium.

When L^1 represents a suitable leaving group such as a halogen atom (eg. fluorine, chlorine) step (iv) typically comprises the use of a suitable base, such as potassium carbonate in a suitable solvent such as dimethylsulfoxide or N,N-dimethylformamide at elevated temperature.

Step (v) is a deprotection reaction where the conditions are dependent upon the nature of the group P^1. Removal of a P^1 tert-butoxycarbonyl group can performed under acidic conditions eg using trifluoroacetic acid in a suitable solvent such as ethyl acetate.

Compounds of formula (IV) may be prepared in accordance with the following procedure:



wherein R^1, R^2, R^3, R^4, m, n, q, L^3 and L^4 are as defined above.

When L^4 represents a suitable leaving group such as a halogen atom (eg. chlorine), step (i) typically comprises the use of suitable base such as potassium carbonate or sodium hydride in a solvent such as dimethylsulfoxide optionally at elevated temperature.

When L^3 represents a suitable leaving group such as a halogen atom (eg. bromine, iodine), step (ii) is typically carried out in a suitable solvent such as dichloromethane optionally at elevated temperature.

Compounds of formula (V), $(V)^a$, (VI), $(VI)^a$ and (XIII) are either known in the literature or can be prepared by analogous methods.

Compounds of formula (I) and their pharmaceutically acceptable salts have affinity for the histamine H3 receptor and are believed to be of potential use in the treatment of neurological diseases including Alzheimer's disease, dementia, age-related memory dysfunction, mild cognitive impairment, cognitive deficit, epilepsy, neuropathic pain, inflammatory pain, Parkinson's disease, multiple sclerosis, stroke and sleep disorders including narcolepsy; psychiatric disorders including schizophrenia (particularly cognitive deficit of schizophrenia), attention deficit hypereactivity disorder, depression and addiction; and other diseases including obesity, asthma, allergic rhinitis, nasal congestion, chronic obstructive pulmonary disease and gastro-intestinal disorders.

Thus the invention also provides a compound of formula (I) or a pharmaceutically acceptable salt thereof, for use as a therapeutic substance in the treatment or prophylaxis of the above disorders, in particular neurodegenerative disorders including Alzheimer's disease.

The invention further provides a method of treatment or prophylaxis of the above disorders, in mammals including humans, which comprises administering to the sufferer

a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

In another aspect, the invention provides the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for use in the treatment of the above disorders.

When used in therapy, the compounds of formula (I) are usually formulated in a standard pharmaceutical composition. Such compositions can be prepared using standard procedures.

Thus, the present invention further provides a pharmaceutical composition for use in the treatment of the above disorders which comprises the compound of formula (I) or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

The present invention further provides a pharmaceutical composition which comprises the compound of formula (I) or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

Compounds of formula (I) may be used in combination with other therapeutic agents, for example histamine H1 antagonists or medicaments claimed to be useful as either disease modifying or symptomatic treatments of Alzheimer's disease. Suitable examples of such other therapeutic agents may be agents known to modify cholinergic transmission such as 5-HT_6 antagonists, M1 muscarinic agonists, M2 muscarinic antagonists or acetylcholinesterase inhibitors. When the compounds are used in combination with other therapeutic agents, the compounds may be administered either sequentially or simultaneously by any convenient route.

The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) or a pharmaceutically acceptable derivative thereof together with a further therapeutic agent or agents.

The combinations referred to above may conveniently be presented for use in the form of a pharmaceutical formulation and thus pharmaceutical formulations comprising a combination as defined above together with a pharmaceutically acceptable carrier or excipient comprise a further aspect of the invention. The individual components of such combinations may be administered either sequentially or simultaneously in separate or combined pharmaceutical formulations.

When a compound of formula (I) or a pharmaceutically acceptable derivative thereof is used in combination with a second therapeutic agent active against the same disease

state the dose of each compound may differ from that when the compound is used alone. Appropriate doses will be readily appreciated by those skilled in the art.

A pharmaceutical composition of the invention, which may be prepared by admixture, suitably at ambient temperature and atmospheric pressure, is usually adapted for oral, parenteral or rectal administration and, as such, may be in the form of tablets, capsules, oral liquid preparations, powders, granules, lozenges, reconstitutable powders, injectable or infusible solutions or suspensions or suppositories. Orally administrable compositions are generally preferred.

Tablets and capsules for oral administration may be in unit dose form, and may contain conventional excipients, such as binding agents, fillers, tabletting lubricants, disintegrants and acceptable wetting agents. The tablets may be coated according to methods well known in normal pharmaceutical practice.

Oral liquid preparations may be in the form of, for example, aqueous or oily suspension, solutions, emulsions, syrups or elixirs, or may be in the form of a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, emulsifying agents, non-aqueous vehicles (which may include edible oils), preservatives, and, if desired, conventional flavourings or colorants.

For parenteral administration, fluid unit dosage forms are prepared utilising a compound of the invention or pharmaceutically acceptable salt thereof and a sterile vehicle. The compound, depending on the vehicle and concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions, the compound can be dissolved for injection and filter sterilised before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, preservatives and buffering agents are dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum. Parenteral suspensions are prepared in substantially the same manner, except that the compound is suspended in the vehicle instead of being dissolved, and sterilisation cannot be accomplished by filtration. The compound can be sterilised by exposure to ethylene oxide before suspension in a sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

The composition may contain from 0.1% to 99% by weight, preferably from 10 to 60% by weight, of the active material, depending on the method of administration. The dose of the compound used in the treatment of the aforementioned disorders will vary in the usual way with the seriousness of the disorders, the weight of the sufferer, and other similar factors. However, as a general guide suitable unit doses may be 0.05 to 1000 mg, more suitably 1.0 to 200 mg, and such unit doses may be administered more than

once a day, for example two or three a day. Such therapy may extend for a number of weeks or months.

The following Descriptions and Examples illustrate the preparation of compounds of the invention.

Description 1
4-[(1-*tert*-Butoxycarbonyl-4-piperidinyl)oxy]pyridine (D1)
To 1-*tert*-butoxycarbonyl-4-hydroxypiperidine (2g) in DMSO (20ml) was added potassium carbonate (2g) followed by 4-chloropyridine (1.3g). The reaction was heated to 70^{0}C for 3h, then cooled and diluted with EtOAc (50ml). The mixture was washed with saturated brine (4x) then evaporated and chromatographed (silica gel; eluting with EtOAc/MeOH, 0-50% MeOH) to give the title compound (D1) as a gum (1.5g).

Description 2
1-Isopropyl-4-(4-piperidinyloxy)piperidine dihydrochloride (D2)
4-[(1-*tert*-Butoxycarbonyl-4-piperidinyl)oxy]pyridine (D1) (0.5g) in DCM (5ml) was treated with isopropyl iodide (2ml). After 2 days the reaction was evaporated from toluene (2x) and then triturated with diethyl ether. The residue was dissolved in MeOH (10ml) containing solid ammonium formate (0.2g), and lithium borohydride (2ml, 1M solution in THF) was added slowly, under an argon stream, with rapid stirring. Then palladium on carbon (0.2g, 10% Pd/C) was added as a slurry in water (2ml), and further lithium borohydride (2ml, 1M solution in THF) was added dropwise. After 2h the reaction was diluted with EtOAc and saturated sodium hydrogen carbonate, and filtered through celite. The EtOAc layer was separated and evaporated to a gum which was dissolved in a small volume of EtOAc and treated with an excess of 95% TFA/water. After 2h toluene was added and the reaction evaporated and then re-evaporated from toluene. The residue was dissolved in EtOAc and treated with HCl (1ml, 1M in diethyl ether). Filtration of the precipitate gave the title compound (D2) (0.5g).

Description 3
1-Benzyl-4-[(1-*tert*-butoxycarbonyl-4-piperidinyl)oxy]pyridinium bromide (D3)
To 4-[(1-*tert*-butoxycarbonyl-4-piperidinyl)oxy]pyridine (D1) (25.47g) in DCM (200ml) was added benzyl bromide (21.91ml). After 4 days the reaction was evaporated and a small volume of DCM added until all solids had dissolved. Diethyl ether was then added and the resultant precipitate was filtered off to give the title compound (D3) as a solid (32.68g).

Description 4
1-*tert*-Butoxycarbonyl-4-(4-piperidinyloxy)piperidine (D4)
To 1-benzyl-4-[(1-*tert*-butoxycarbonyl-4-piperidinyl)oxy]pyridinium bromide (D3) (15g) in MeOH (500ml) was slowly added lithium borohydride (100ml, 2M solution in THF) under

a stream of argon whilst the temperature was kept below 30^{0}C. After 2h formic acid was added (30ml) until pH~4. Ammonium formate (50g) in MeOH (100ml) was added as a slurry followed by palladium on carbon (2g, 10% Pd/C). After 2 days the reaction was filtered and evaporated, redissolved in EtOAc (400ml) and washed with saturated sodium hydrogen carbonate solution and brine. The organic layer was dried ($MgSO_4$), evaporated, and redissolved in MeOH (200ml). Acetic acid (20ml) was added followed by Pd on carbon (2g, 10% Pd/C), and the reaction hydrogenated at rt for 16h followed by 80^{0}C for 2h. The reaction mixture was filtered, evaporated, redissolved in EtOAc (300ml) and washed with saturated sodium hydrogen carbonate solution, followed by brine, before being dried ($MgSO_4$) and evaporated to give the title compound (D4) as an oil (1.75g).

Description 5

1-Cyclobutyl-4-[(1-*tert*-butoxycarbonyl-4-piperidinyl)oxy]piperidine (D5)

To 1-*tert*-butoxycarbonyl-4-(4-piperidinyloxy)piperidine (D4) (7.0g) and triethylamine (6.9ml) in DCM (300ml) was added cyclobutyl ketone and after 5min sodium triacetoxyborohydride (10.46g) was added. After 16h the reaction was washed with a solution of saturated potassium carbonate (2x200ml) and brine (200ml). The organic layer was dried ($MgSO_4$) and evaporated to give the title compound (D5) as a white solid (8.11g).

Description 6

1-Cyclobutyl-4-(4-piperidinyloxy)piperidine (D6)

1-Cyclobutyl-4-[(1-*tert*-butoxycarbonyl-4-piperidinyl)oxy]piperidine (D5) (8.11g) was stirred in a solution of HCl (200ml, 4M in dioxan) and MeOH (200ml) for 3h. The solvent was removed by evaporation and the residue treated with saturated potassium carbonate solution (250ml) and extracted into DCM (3x300ml). The combined organic extracts were dried ($MgSO_4$) and evaporated to give the title compound (D6) as a pale yellow oil which crystallised upon standing (5.31g).

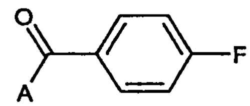
Description 7

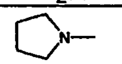
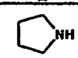
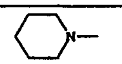
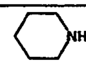
4-(4-Fluorobenzoyl)-morpholine (D7)

EDC (8.86g) was added to a solution of 4-fluorobenzoic acid (5.0g), morpholine (3.72ml), HOBt (4.82g) and triethylamine (12.41ml) in DMF (300ml) and stirred at room temperature for 18h. After removal of the solvent by evaporation, the residue was redissolved in DCM (100ml) and washed with saturated sodium hydrogen carbonate solution (2x50ml) and brine (50ml) before drying over $MgSO_4$ to give the title compound (D7) (6.63g).

Descriptions 8-11 (D8-D11)

Descriptions 8-11 were prepared from 4-fluorobenzoic acid and the appropriate amine using the procedure described in Description 7.



Description	A	Amine	Mass Spectrum (ES+)
D8	MeNH-	$MeNH_2$	$[MH]^+$ 154
D9	Me_2N-	Me_2NH	$[MH]^+$ 168
D10			$[MH]^+$ 194
D11			$[MH]^+$ 208

Description 12

4-(4-Bromophenyl)-2-methyl-oxazole (D12)

4-Bromophenacyl bromide (21.3g) and acetamide (11.3g) were heated together at 130°C under argon. After 2.5h the reaction mixture was allowed to cool, and partitioned between water (150ml) and Et_2O (150ml). The organic phase was washed with aqueous NaOH (0.5N), aqueous HCl (0.5M) and saturated brine (100ml of each), dried ($MgSO_4$) and evaporated to give a brown solid which was recrystallised from hexanes to give the title compound (D12) as an orange solid (4.1g). LCMS electrospray (+ve) 239 (MH^+).

Description 13

5-(4-Bromophenyl)-2-methyl-oxazole (D13)

Trifluoromethanesulfonic acid (6.6ml) was added to a flask containing iodobenzene diacetate (12.2g) and MeCN (200ml) at rt. After 25min a solution of 4'-bromoacetophenone (5g) in MeCN (50ml) was added and the resultant mixture heated at reflux for 6h. The reaction was allowed to cool to rt before the solvent was evaporated and the residue partitioned between saturated aqueous sodium hydrogen carbonate (150ml) and EtOAc (150ml). The organic phase was washed with saturated brine (150ml), dried ($MgSO_4$) and evaporated to give an orange solid. The crude product was purified by column chromatography (silica gel, 50% EtOAc in hexanes) to give the title compound (D13) as a pale yellow solid (3.5g). LCMS electrospray (+ve) 239 (MH^+).

Description 14

5-(4-Bromophenyl)-3-methyl isoxazole (D14)

A solution of n-BuLi (81ml of a 1.6M solution in hexanes) was added to a solution of acetone oxime (4.85g) in THF (100ml) at 0°C. The reaction mixture was allowed to warm to rt over 1h. A solution of methyl 4-bromobenzoate (9.4g) in THF (30ml) was then added to the reaction mixture and allowed to stir for 24h. Water (50ml) was added to the reaction, the organics were separated and evaporated to give a brown oil, which was further evaporated from toluene (2×25ml). The crude product was purified by column

chromatography (silica gel, 10-25% gradient of EtOAc in hexanes) to give the title compound (D14) as a pale yellow solid (5.4g). LCMS electrospray (+ve) 239 (MH^+).

Description 15

3-(4-Bromophenyl)-5-methyl-1,2,4-oxadiazole (D15)

Step 1: 4-Bromo-N-hydroxy-benzenecarboximidamide

4-Bromophenylcarbonitrile (10.2g), hydroxylamine hydrochloride (7.8g) and Triethylamine (11.3g) were dissolved in EtOH (250ml) and the reaction mixture was heated at reflux for 3h, after which it was evaporated to form a white precipitate of the desired amidoxime, which was filtered and washed with water (25ml). The filtrate was extracted into EtOAc (2×25ml), and the combined organic extracts were dried (Na_2SO_4) and evaporated to give a second crop of the subtitle compound (combined yield = 11.1g). LCMS electrospray (+ve) 216 (MH^+).

Step 2: 3-(4-Bromophenyl)-5-methyl-1,2,4-oxadiazole

The product from D15 step 1 was suspended in acetic anhydride and heated to 100°C for 4h, then 120°C for 3h. After cooling the reaction mixture was evaporated to give a brown solid. This was partitioned between saturated aqueous sodium hydrogen carbonate and EtOAc. The organic phase was washed with saturated brine, dried (Na_2SO_4) and evaporated to give a yellow solid. The crude product was purified by column chromatography (silica gel, 10-100% gradient of EtOAc in hexanes) to give the title compound (D15) as a white solid (6.2g). LCMS electrospray (+ve) 240 (MH^+).

Description 16

5-(4-Bromophenyl)-3-methyl-1,2,4-oxadiazole (D16)

4-Bromobenzamide (5.3g) and dimethylformamide dimethoxyacetal (35ml) were heated together at 125°C for 2h. The reaction was allowed to cool to rt and the liquid evaporated to give a pale yellow solid. Hydroxylamine hydrochloride (2.2g) in 1N NaOH solution (36ml) was added, followed by dioxane (36ml) then AcOH (48ml). The reaction mixture was stirred at rt for 30min then heated at 90°C for 3h. The reaction was allowed to cool to rt and saturated aqueous K_2CO_3 solution (100ml) was added followed by DCM (200ml) before filtering. The organic phase was separated from the mixture; then saturated brine (100ml) was added and the aqueous phase was extracted into EtOAc (200ml). The combined organic phases were dried (Na_2SO_4) and evaporated to give a brown solid. The crude product was purified by column chromatography (silica gel, step gradient 10-50% EtOAc in hexanes) to give the title compound (D16) as a white solid (2.9g). LCMS electrospray (+ve) 240 (MH^+).

Description 17

2-(4-Bromophenyl)-oxazole (D17)

Step 1: 4-Bromo-N-(2,2-dimethoxyethyl)-benzamide

Potassium carbonate (8.0g) was added to a solution of 2,2-dimethoxyethylamine in water (90ml) and acetone (40ml) at rt. The reaction mixture was cooled in an ice-water

bath and 4-bromobenzoyl chloride (16.4g) dissolved in acetone (70ml) was added drop-wise over 90min. The stirred reaction mixture was allowed to warm to rt. After a further 2h the reaction mixture was extracted into EtOAc (3×75ml), the combined organics were washed with saturated aqueous sodium hydrogen carbonate , dried ($MgSO_4$) and evaporated to give the amide as an off white solid (18.5g). LCMS electrospray (+ve) 289 (MH^+).

Step 2: 2-(4-Bromophenyl)-oxazole

The product of D17 step 1 was suspended in Eaton's reagent (200ml), the reaction mixture was purged with argon and heated to 240°C for 9h. The reaction mixture was then allowed to cool and stirred for 65h at rt. The crude mixture was poured over ice (1L) and stirred for 1h. The aqueous mixture was extracted into EtOAc (2×250ml), dried ($MgSO_4$) and evaporated to give a grey powder. This crude solid was dissolved in THF (300ml) and EtOH (300ml), and Hunig's base (21.1ml) was added. MP-carbonate resin (40.1g) and PS-thiophenol resin (69.7g) were suspended in the reaction mixture, which was stirred for 24h. The suspension was filtered and the solid phase resins washed with 1:1 THF:EtOH (3×600ml), and the combined organics evaporated to give the title compound (D17) as a white solid (9.0g). LCMS electrospray (+ve) 225 (MH^+).

Description 18

5-Bromo-*N,N*-dimethyl-2-pyridinecarboxamide (D18)

Step 1: 5-Bromo-2-pyridinecarboxylic acid

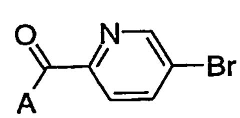
5-Bromo-2-pyridinecarbonitrile (5.0g) was heated at reflux in conc. HCl (75ml) for 4.5h. The reaction was allowed to cool to room temperature and the precipitate filtered to give the subtitle compound as a white solid (3.5g). The filtrate was extracted into diethyl ether (3×200ml), and the solvent was evaporated to give a second crop of the subtitle compound (1.30g).

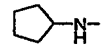
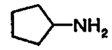
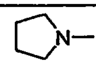
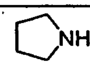
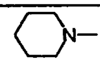
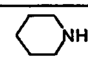
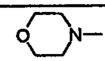
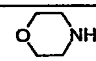
Step 2: 5-Bromo-*N,N*-dimethyl-2-pyridinecarboxamide

The product of D18 step 1 was added to a solution of EDC (1.10g), dimethylamine hydrochloride (0.46g), HOBt (0.50g) and triethylamine (2.10ml) in DMF (70ml) and stirred at rt for 18h. After removal of the solvent by evaporation, the residue was redissolved in DCM (50ml) and washed with saturated sodium hydrogen carbonate (2×25ml), brine (25ml) and dried (Na_2SO_4) to give the crude carboxamide. Purification by chromatography [silica gel, eluting with ethyl acetate/hexanes, 0-100%] gave the title compound (D18) (0.58g).

Descriptions 19-26 (D19-26)

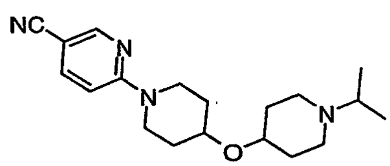
Descriptions 19-26 were prepared from 5-bromo-2-pyridinecarboxylic acid (Description 18, step 1) and the appropriate amine using the procedure of Description 18, step 2.



Description	A	Amine	Mass Spectrum (ES+)
D19	MeNH-	$MeNH_2$	$[MH]^+$ 216
D20	EtNH-	$EtNH_2$	$[MH]^+$ 230
D21	n-PrNH-	n-$PrNH_2$	$[MH]^+$ 244
D22	i-PrNH-	i-$PrNH_2$	$[MH]^+$ 244
D23			$[MH]^+$ 270
D24			$[MH]^+$ 256
D25			$[MH]^+$ 270
D26			$[MH]^+$ 272

Example 1

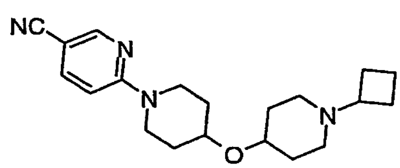
4-{[1-(5-Cyano-2-pyridyl)-4-piperidinyl]oxy}-1-isopropyl-piperidine hydrochloride (E1)



1-Isopropyl-4-(4-piperidinyloxy)piperidine dihydrochloride (D2) (0.25g) in DMSO (3ml) was treated with 2-chloro-5-cyano-pyridine (0.23g) and potassium carbonate (0.23g). The reaction was heated to 100°C for 3h then cooled and diluted with EtOAc and saturated sodium hydrogen carbonate solution. The EtOAc layer was separated, evaporated, and an aliquot processed on a mass directed autoprep HPLC system. The fractions with the correct mass were combined, evaporated from toluene, and dissolved in a small volume of EtOAc before addition of HCl (1ml, 1M in diethyl ether). The precipitate was filtered and washed with diethyl ether before being dried under vacuum to give the title compound (E1) as a solid (23mg). LCMS electrospray (+ve ion) 329 (MH^+); ^{1}H NMR δ(CD_3OD) 1.37 (6H, m), 1.84 (3H, m), 2.06 (4H, m), 2.3 (1H, m), 3.21 (3H, m), 3.5 (2H, m), 3.78 (3H, m), 3.97 (3H, m), 7.52 (1H, br d, J=14.5Hz), 8.09 (1H, m), and 8.48 (1H, d, J=1.8Hz).

Example 2

4-{[1-(5-Cyano-2-pyridyl)-4-piperidinyl]oxy}-1-cyclobutyl-piperidine hydrochloride (E2)



Step 1: 4-{[1-(5-Cyano-2-pyridyl)-4-piperidinyl]oxy}-1-*tert*-butoxycarbonyl-piperidine

1-*tert*-Butoxycarbonyl-4-(4-piperidinyloxy)piperidine (D4) (0.118g) was reacted with 2-chloro-5-cyano-pyridine (0.0573g) in DMSO (5ml) containing potassium carbonate (0.069g) for 4h at 60^{0}C. The reaction was then evaporated to a minimum volume and the residue redissolved in DCM (20ml) and washed with saturated sodium hydrogen carbonate solution. Evaporation of the dried ($MgSO_4$) organic layer provided the subtitle compound as an oil which crystallised on standing (0.191g).

Step 2: 4-{[1-(5-Cyano-2-pyridyl)-4-piperidinyl]oxy}piperidine hydrochloride

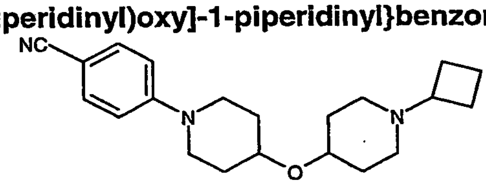
To the product of E2 step 1 (0.191g) in DCM (5ml) was added HCl in dioxan (5ml, 4M). Evaporation of the solvent from DCM gave the subtitle compound (0.141g).

Step 3: 4-{[1-(5-Cyano-2-pyridyl)-4-piperidinyl]oxy}-1-cyclobutyl-piperidine hydrochloride

To the product of E2 step 2 (0.141g) in DCM (5ml) was added triethylamine (0.205ml) and cyclobutyl ketone (0.073ml), and after 5min sodium triacetoxyborohydride (0.208g) was added. After 2 days the reaction was diluted with DCM (10ml) and washed with a solution of potassium carbonate (2x10ml) and brine (10ml). The organic layer was dried ($MgSO_4$) and evaporated and the residue chromatographed [silica gel, eluting with (10%NH_3 in MeOH)/DCM, 0-10%]. The residue was evaporated from toluene and dissolved in DCM to which was added HCl (0.5ml, 1M in diethyl ether). This was evaporated and co-evaporated from acetone (3x) and then triturated from acetone – diethyl ether to give the title compound (E2) (0.063g). LCMS electrospray (+ve ion) 341 (MH^+), ^1H NMR δ(CD_3OD) 1.4 (2H, m), 1.6-2 (7H, m), 2.12 (2H, m), 2.3 (2H, m), 2.79 (2H, m), 3.11 (1H,br d, J=2.8 Hz), 3.35 (3H, m), 3.7 (4H, m), 4.0 (2H, m), 6.95 (1H, dd, J=2.8 and 9.2 Hz), 7.82 (1H, m) and 8.46 (1H, br s).

Example 3

4-{4-[(1-Cyclobutyl-4-piperidinyl)oxy]-1-piperidinyl}benzonitrile hydrochloride (E3)



Step 1: 4-{4-[(1-*tert*-Butoxycarbonyl-4-piperidinyl)oxy]-1-piperidinyl}benzonitrile

1-*tert*-Butoxycarbonyl-4-(4-piperidinyloxy)piperidine (D4) (0.340g) was reacted with 4-fluorobenzonitrile (0.218g) in DMSO (10ml) containing potassium carbonate (0.331g) for 5h at 120^{0}C. The reaction was then evaporated to a minimum volume and the residue redissolved in EtOAc (50ml) and washed with saturated sodium hydrogen carbonate (3x30ml) and saturated brine (30ml). Evaporation of the dried ($MgSO_4$) organic layer provided the subtitle compound as a pale yellow solid (0.422g).

Step 2: 4-{4-[(4-Piperidinyl)oxy]-1-piperidinyl}benzonitrile hydrochloride

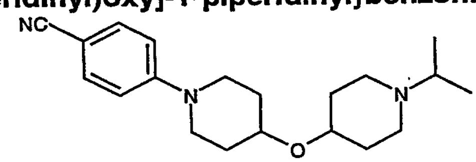
To the product of E3 step 1 (0.422g) in methanol (10ml) was added HCl in dioxan (10ml, 4M). After 3h evaporation of the solvent gave the subtitle compound (0.466g).

Step 3: 4-{4-[(1-Cyclobutyl-4-piperidinyl)oxy]-1-piperidinyl}benzonitrile hydrochloride

To the product of E3 step 2 (0.150g) in DCM (10ml) was added triethylamine (0.077ml) and cyclobutyl ketone (0.070ml), and after 5min sodium triacetoxyborohydride (0.197g) was added. After 18h the reaction was diluted with DCM (10ml) and washed with K_2CO_3 solution (3x20ml). The organic layer was dried ($MgSO_4$) and evaporated and the residue chromatographed [silica gel, eluting with (10%NH_3 in MeOH)/DCM, 0-10%]. The free base product was evaporated from toluene and dissolved in DCM (5ml) to which was added HCl (1ml, 1M in diethyl ether). This was evaporated and co-evaporated from acetone (3x) and then recrystallised from acetone to give the title compound (E3) (0.063g). MS electrospray (+ion) 341 (MH^+).^{1}H NMR δ (DMSO-d6): 10.45 (1H, s), 8.46 (1H, s), 7.83 (1H, m), 6.96 (1H, dd, J=9.2Hz, 2.4Hz) , 4.03-3.50 (6H, m, plus HOD), 3.47-3.25 (3H, m), 3.17 (1H, m), 2.90-2.66 (2H, m), 2.30 (2H, m), 2.18-1.99 (2H, m), 1.98-1.58 (7H, m), 1.45 (2H, m).

Example 4

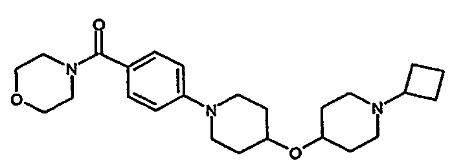
4-{4-[(1-Isopropyl-4-piperidinyl)oxy]-1-piperidinyl}benzonitrile hydrochloride (E4)



1-Isopropyl-4-(4-piperidinyloxy)piperidine dihydrochloride (D2) (0.25g) in DMSO (3ml) was treated with 4-fluorobenzonitrile (0.2g) and potassium carbonate (0.23g). The reaction was heated to 100^{0}C for 3h then cooled and diluted with EtOAc and saturated sodium hydrogen carbonate solution. The EtOAc layer was separated, evaporated, and an aliquot processed on a mass directed autoprep HPLC system. The fractions with the correct mass were combined, evaporated from toluene, and dissolved in a small volume of EtOAc before addition of HCl (1ml, 1M in diethyl ether). The precipitate was filtered and washed with diethyl ether before being dried under vacuum to give the title compound (E4) as a solid (28mg). LCMS electrospray (+ve ion) 328 (MH^+); ^{1}H NMR δ (DMSO-d6) 1.23 (6H, m), 1.46 (2H, m), 1.88 (3H, m), 2.06 (2H, m), 3.05 (2H, m), 3.14 (3H, m), 3.42 (2H, m), 3.72 (3H, m), 4.2 (2H, obscured by H2O), 7.02 (2H, d, J=8.8Hz), 7.55 (2H, d, J=8.8Hz).

Example 5

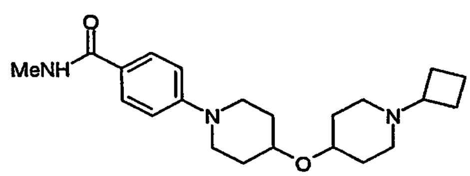
4-[(4-{4-[(1-Cyclobutyl-4-piperidinyl)oxy]-1-piperidinyl}phenyl)carbonyl]morpholine hydrochloride (E5)



1-Cyclobutyl-4-(4-piperidinyloxy)piperidine (D6) (0.250g), 4-(4-fluorobenzoyl)-morpholine (D7) (0.330g) and anhydrous potassium carbonate (0.290g) were added to a 5ml Personal Chemistry microwave vial, to which DMSO (3ml) was added. The vial was sealed and heated at 230°C for 30min in an Emrys Optimizer microwave reactor. The crude reaction mixture was passed through an SCX cartridge (20g, MeOH (80ml) then 2N NH_3 in MeOH (80ml). Purification by chromatography [silica gel, eluting with (10%NH_3 in MeOH)/DCM, 0-10%] and treatment of the free base product dissolved in DCM (5ml) with HCl (1ml, 1M in diethyl ether), followed by evaporation and co-evaporation from acetone (3x) gave the title compound (E5) as a crystalline solid (0.125g). MS electrospray (+ion) 426 (MH^+). ^1H NMR δ (DMSO-d6): 10.78 (1H, m), 7.33-6.91 (4H, m), 3.90-2.99 (11H, m, plus HOD), 2.88-2.63 (2H, m), 2.35 (2H, m), 2.12 (3H, m), 1.91 (4H, m), 1.82-1.41 (13H, m).

Example 6

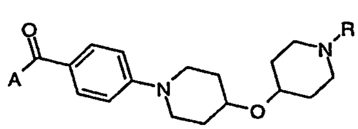
4-{4-[(1-Cyclobutyl-4-piperidinyl)oxy]-1-piperidinyl}-*N*-methylbenzamide hydrochloride (E6)

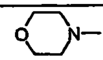
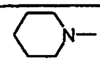
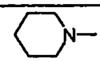
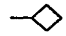
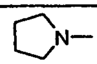
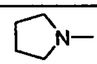
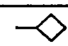
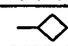
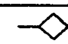


1-Cyclobutyl-4-(4-piperidinyloxy)piperidine (D6) (0.100g), 4-fluoro-*N*-methyl benzamide (D8) (0.088g) and anhydrous potassium carbonate (0.121g) were added to a 5ml Personal Chemistry microwave vial, to which DMSO (2ml) was added. The vial was sealed and heated at 230°C for 30min in an Emrys Optimizer microwave reactor. The crude reaction mixture was passed through an SCX cartridge [20g, MeOH (80ml) then 2N NH_3 in MeOH (80ml)]. Purification by chromatography [silica gel, eluting with (10%NH_3 in MeOH)/DCM, 0-10%] and treatment of the free base product dissolved in DCM (5ml) with HCl (1ml, 1M in diethyl ether), followed by evaporation and co-evaporation from acetone (3x) gave the title compound (E6) as a crystalline solid (0.074g). MS electrospray (+ion) 372 (MH^+). ^1H NMR δ (DMSO-d6): 8.17 (1H, s), 7.72 (dd, 2H, J=9.2, 2.8), 7.04 (2H, s), 4.32-2.81 (11H, m, plus HOD), 2.74 (3H, s), 2.34 (2H, m), 2.15 (2H, m), 2.00-1.40 (10H, m)

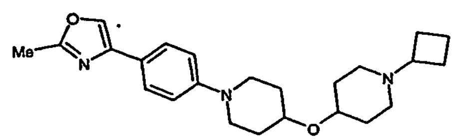
Examples 7-15 (E7-E15)

Examples 7-15 were prepared in a similar manner to Example 6 from either 1-isopropyl-4-(4-piperidinyloxy)piperidine (free base from D2) or 1-cyclobutyl-4-(4-piperidinyloxy) piperidine (D6) and the appropriate 4-fluorobenzamide (D7-D11). All compounds displayed ^1H NMR and mass spectral data that were consistent with structure.



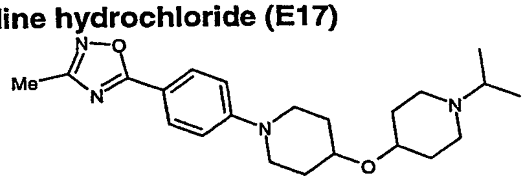
Example	A	R	Mass Spectrum (ES+)
E7		i-Pr	[MH]+ 416
E8		i-Pr	[MH]+ 414
E9			[MH]+ 425
E10		i-Pr	[MH]+ 400
E11			[MH]+ 412
E12	Me_2N-	i-Pr	[MH]+ 374
E13	Me_2N-		[MH]+ 386
E14	MeNH-	i-Pr	[MH]+ 360
E15	MeNH-		[MH]+ 386

Example 16
1-Cyclobutyl-4-({1-[4-(2-methyl-1,3-oxazol-4-yl)phenyl]-4-piperidinyl}oxy)piperidine hydrochloride (E16)



Sodium *tert*-butoxide (0.064g) was added to a solution of 1-cyclobutyl-4-(4-piperidinyloxy)piperidine (D6) (0.105g), 4-(4-bromophenyl)-2-methyl-oxazole (D12) (0.095g) and acetato(2'-di-*tert*-butylphosphino-1,1'-biphenyl-2-yl)palladium (II) (0.004g) in toluene (2ml). The reaction was heated to 60°C for 4h, then at 40°C for 1.5h, then at 55°C for a further 16h. The reaction mixture was diluted with toluene (5ml), and Argonaught MP-NCO resin (1g) was added and the mixture stirred for 1h at 55°C. The reaction mixture was loaded directly onto silica and purified by chromatography [silica gel, eluting with (10% NH_3 in MeOH)/DCM, 0-10%]. The purified residue was evaporated from toluene and dissolved in DCM (5ml) to which was added HCl (1ml, 1M in diethyl ether). Evaporation of the solvent gave the title compound (E16) (0.056g). MS electrospray (+ion) 396 (MH^+). ^1H NMR δ (DMSO-d6): 10.71 (1H, s), 8.14 (1H, m), 7.75-7.43 (4H, m), 4.05-3.50 (6H, m, plus HOD), 3.38-3.10 (4H, m), 2.91-2.66 (2H, m), 2.45 (3H, s), 2.35 (2H, m), 2.20-1.58 (11H, m).

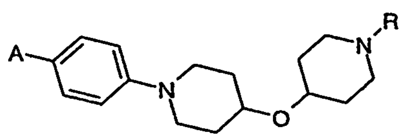
Example 17
1-(1-Methylethyl)-4-({1-[4-(3-methyl-1,2,4-oxadiazol-5-yl)phenyl]-4-piperidinyl}oxy)piperidine hydrochloride (E17)

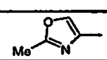
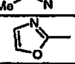
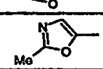
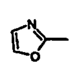
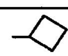
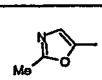
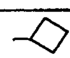
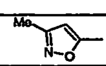
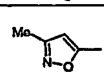
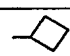
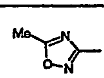


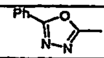
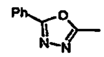
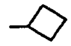
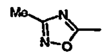
Sodium *tert*-butoxide (0.058g) was added to a solution of 1-isopropyl-4-(4-piperidinyloxy)piperidine (free base from D2) (0.10g), 5-(4-bromophenyl)-3-methyl-1,2,4-oxadiazole (D16) (0.096g) and acetato(2'-di-*tert*-butylphosphino-1,1'-biphenyl-2-yl)palladium(II) (0.004g) in toluene (3ml). The reaction was heated to 60°C for 6h, then a further charge of acetato(2'-di-*tert*-butylphosphino-1,1'-biphenyl-2-yl)palladium(II) (0.004g) was added followed by heating at 70°C for a further 16h. The reaction mixture was diluted with toluene (5ml), and Argonaught MP-NCO resin (1g) was added and the mixture stirred for 1h. After evaporation, the crude residue was diluted with MeOH (5ml) and passed through an SCX cartridge [10g, MeOH (80ml) then 2N NH_3 in MeOH (80ml)]. Purification by chromatography [silica gel, eluting with (10%NH_3 in MeOH)/DCM, 0-10%] and treatment of the free base product dissolved in DCM (5ml) with HCl (1ml, 1M in diethyl ether), followed by evaporation afforded the title compound (E17) (0.054g). MS electrospray (+ion) 385 (MH^+). ^{1}H NMR δ (DMSO-d6): 10.05 (1H, m), 7.87 (2H, d, J=8.4Hz), 7.10 (2H, d, J=7.6Hz), 3.90-3.61 (4H, m, plus HOD), 3.47-3.28 (2H, m), 3.18 (3H, m), 3.06-2.87 (2H, m), 2.35 (3H, s), 2.12-1.70 (6H, m), 1.51 (2H, m), 1.25 (6H, m).

Examples 18-28 (E18-E28)

Examples 18-28 were prepared in a similar manner to Example 17 from either 1-isopropyl-4-(4-piperidinyloxy)piperidine (free base from D2) or 1-cyclobutyl-4-(4-piperidinyloxy) piperidine (D6) and the appropriate 4-bromophenyl precursor (D12-D17). All compounds displayed ^{1}H NMR and mass spectral data that were consistent with structure.

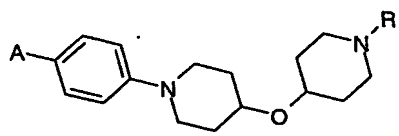


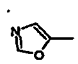
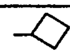
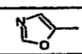
Example	A	R	Mass Spectrum (ES+)
E18		i-Pr	$[MH]^+$ 384
E19		i-Pr	$[MH]^+$ 370
E20		i-Pr	$[MH]^+$ 384
E21			$[MH]^+$ 382
E22			$[MH]^+$ 396
E23		i-Pr	$[MH]^+$ 384
E24			$[MH]^+$ 396
E25			$[MH]^+$ 397

E26		i-Pr	$[MH]^+$ 447
E27			$[MH]^+$ 459
E28			$[MH]^+$ 397

Examples 29-30 (E29-E30)

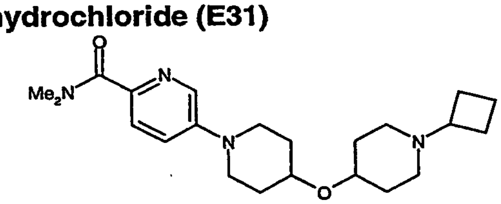
Examples 29-30 were prepared in a similar manner to Example 6 from either 1-isopropyl-4-(4-piperidinyloxy)piperidine (free base from D2) or 1-cyclobutyl-4-(4-piperidinyloxy) piperidine (D6) and commercially available 5-(4-fluorophenyl)-oxazole. All compounds displayed ^{1}H NMR and mass spectral data that were consistent with structure.



Example	A	R	Mass Spectrum (ES^+)
E29			$[MH]^+$ 382
E30		i-Pr	$[MH]^+$ 370

Example 31

5-{4-[(1-Cyclobutyl-4-piperidinyl)oxy]-1-piperidinyl}-*N,N*-dimethyl-2-pyridinecarboxamide hydrochloride (E31)

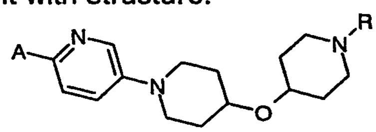


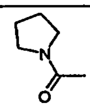
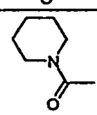
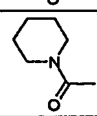
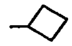
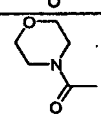
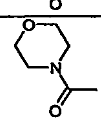
Palladium (II) acetate (0.002g) and sodium *tert*-butoxide (0.050g) were added to an argon-filled round bottom flask, followed by toluene (2ml). 1-Cyclobutyl-4-(4-piperidinyloxy)piperidine (D6) (0.100g), 5-bromo-*N,N*-dimethyl-2-pyridinecarboxamide (D18) and 2,8,9-triisobutyl-2,5,8,9-tetraaza-1-phosphabicyclo[3.3.3]undecane (0.005g) were added and the reaction mixture heated at 80°C for 2h. The crude reaction mixture was passed through an SCX cartridge [20g, MeOH (80ml) then 2N NH_3 in MeOH (80ml)]. Chromatography [silica gel, eluting with (10% NH_3 in MeOH)/DCM, 0-10%] and treatment of the free base product dissolved in DCM (5ml) with HCl (1ml, 1M in diethyl ether), followed by evaporation gave the title compound (E31) (0.085g). MS electrospray (+ion) 387 (MH^+). ^{1}H NMR δ (DMSO-d6): 10.92 (1H, m), 8.29 (1H, s), 7.53 (2H,

m),4.59-3.49 (5H, m, plus HOD),.3.31 (1H, m), 3.15 (3H, m), 3.07 (3H, s), 3.01 (3H, s), 2.78 (2H, m), 2.33 (3H, m), 2.20-1.42 (11H, m).

Examples 32-37 (E32-37)

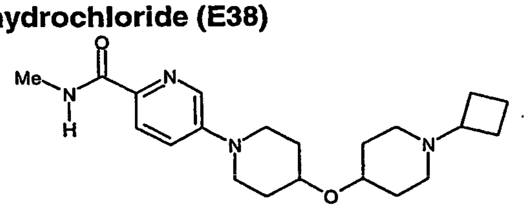
Examples 32-37 were prepared in a similar manner to Example 31 from either 1-isopropyl-4-(4-piperidinyloxy)piperidine (free base from D2) or 1-cyclobutyl-4-(4-piperidinyloxy) piperidine (D6) and the appropriate 2-pyridine-carboxamide precursor (D18 and D24-D26). All compounds displayed ^{1}H NMR and mass spectral data that were consistent with structure.



Example	A	R	Mass Spectrum (ES$^+$)
E32	-CONMe$_2$	i-Pr	$[MH]^+$ 375
E33		i-Pr	$[MH]^+$ 401
E34		i-Pr	$[MH]^+$ 415
E35			$[MH]^+$ 427
E36		i-Pr	$[MH]^+$ 417
E37			$[MH]^+$ 429

Example 38

5-{4-[(1-Cyclobutyl-4-piperidinyl)oxy]-1-piperidinyl}-*N*-methyl-2-pyridinecarboxamide hydrochloride (E38)

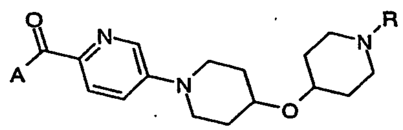


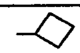
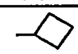
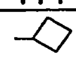
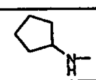
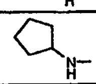
1-Cyclobutyl-4-(4-piperidinyloxy)piperidine (D6) (0.150g), 5-bromo-*N*-methyl-2-pyridinecarboxamide (D19) (0.203g) and anhydrous potassium carbonate (0.174g) were added to a 5ml Personal Chemistry microwave vial, to which DMSO (2ml) was added. The vial was sealed and heated at 250°C for 30min in an Emrys Optimizer microwave

reactor. The crude mixture was diluted with MeOH (5ml) and passed through an SCX cartridge [10g, MeOH (80ml) then 2N NH_3 in MeOH (80ml)]. The eluted mixture was evaporated, then chromatography [silica gel, eluting with (10%NH_3 in MeOH)/DCM, 0-10%] and treatment of the free base product dissolved in DCM (5ml) with HCl (1ml, 1M in diethyl ether), followed by evaporation gave the title compound (E38) (0.015g). MS electrospray (+ion) 373 (MH^+). ^1H NMR δ (CDCl3): 8.16 (1H, d, J=2.8Hz), 8.02 (1H, d, J=8.8Hz), 7.76 (1H, d, J=5.6Hz), 7.21 (1H, dd, J=8.8Hz, J=2.8Hz), 3.64 (3H, m), 3.46 (1H, m), 3.13 (2H, m), 2.99 (3H, d, J=5.2Hz), 2.68 (3H, m), 2.09-1.78 (10H, m), 1.74-1.52 (6H, m, plus HOD).

Examples 39-46 (E39-46)

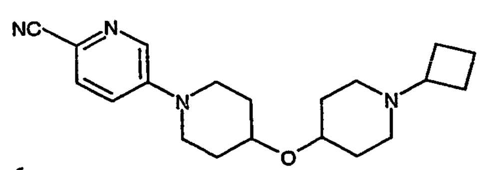
Examples 39-46 were prepared in a similar manner to Example from either 1-isopropyl-4-(4-piperidinyloxy)piperidine (free base from D2) or 1-cyclobutyl-4-(4-piperidinyloxy) piperidine (D6) and the appropriate 2-pyridine-carboxamide precursor (D20-23). All compounds displayed ^1H NMR and mass spectral data that were consistent with structure.



Example	A	R	Mass Spectrum (ES+)
E39	EtNH-	i-Pr	[MH]+ 375
E40	EtNH-		[MH]+ 387
E41	n-PrNH-	i-Pr	[MH]+ 389
E42	n-PrNH-		[MH]+ 401
E43	i-PrNH-	i-Pr	[MH]+ 389
E44	i-PrNH-		[MH]+ 401
E45		i-Pr	[MH]+ 415
E46			[MH]+ 427

Example 47

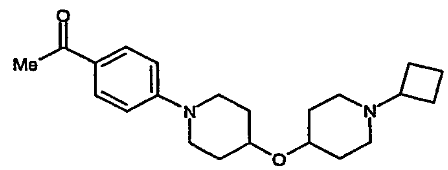
5-{4-[(1-Cyclobutyl-4-piperidinyl)oxy]-1-piperidinyl}-2-pyridinecarbonitrile hydrochloride (E47)



1-Cyclobutyl-4-(4-piperidinyloxy)piperidine (D6) (0.210g), 5-bromo-2-pyridinecarbonitrile (0.194g) and anhydrous potassium carbonate (0.244g) were added to a 5ml Personal Chemistry microwave vial, to which DMSO (2ml) was added. The vial was sealed and heated at 140°C for 15min in an Emrys Optimizer microwave reactor. The reaction mixture was evaporated to dryness, DCM (10ml) was added followed by Argonaught MP-NCO resin (1.0g) and the mixture allowed to stir for 16h. The crude mixture was passed through an SCX cartridge (10g, eluting with MeOH (80ml) then 2N NH_3 in MeOH (80ml). The eluted mixture was evaporated and re-evaporated from toluene (20ml). Chromatography [silica gel, eluting with (10%NH_3 in MeOH)/DCM, 0-10%] and treatment of the free base product dissolved in DCM (5ml) with HCl (1ml, 1M in diethyl ether), followed by evaporation gave the title compound (E47) (0.10g). MS electrospray (+ion) 341 (MH^+). ^1H NMR δ (DMSO-d6): 10.38 (1H, s), 8.42 (1H, m), 7.72 (1H, d, J=9.2Hz), 7.38 (1H, m), 3.91-3.48 (6H, m), 3.31-3.10 (3H, m), 2.89-2.62 (2H, m), 2.38-1.41 (14H, m).

Example 48

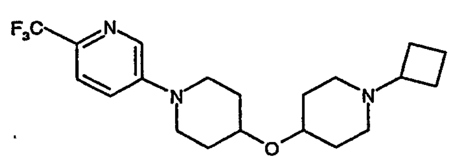
1-(4-{4-[(1-Cyclobutyl-4-piperidinyl)oxy]-1-piperidinyl}phenyl)ethanone hydrochloride (E48)



4'-Bromoacetophenone (0.102g), tris(dibenzylideneacetone)dipalladium(0) (0.025g) and 2-dicyclohexylphosphino-2'-(N,N-dimethylamino)biphenyl (0.059g) were added to degassed dioxane (5ml). After 15 min 1-cyclobutyl-4-(4-piperidinyloxy)piperidine (D6) (0.10g) and sodium *tert*-butoxide (0.061g) were added and the reaction mixture heated at 80°C for 3h, then heated at 100°C for 1h. After diluting with MeOH (5ml) the crude mixture was passed through an SCX cartridge [10g, MeOH (80ml) then 2N NH_3 in MeOH (80ml)]. Chromatography [silica gel, eluting with (10%NH_3 in MeOH)/DCM, 0-10%] and treatment of the free base product in DCM (5ml) with HCl (1ml, 1M in diethyl ether), followed by evaporation gave the title compound (E48) (0.10g). MS electrospray (+ion) 357 (MH^+). ^1H NMR δ (DMSO-d6): 7.80 (2H, dd, J=8.8, 1.2), 7.00 (2H, dd, J=8.8, 2.8), 3.78-3.46 (5H, m), 3.35-3.07 (4H, m), 2.87-2.64 (2H, m), 2.43 (3H, s), 2.41-2.39 (2H, m), 2.20-2.10 (2H, m), 2.08-1.81 (5H, m), 1.78-1.60 (3H, m), 1.57-1.42 (2H, m).

Example 49

5-{4-[(1-Cyclobutyl-4-piperidinyl)oxy]-1-piperidinyl}-2-(trifluoromethyl)pyridine hydrochloride (E49)



5-Bromo-2-trifluoromethylpyridine (F. Cottet and M. Schlosser, Eur. J. Org. Chem., 2002, 327) (0.187g), tris(dibenzylideneacetone)dipalladium(0) (0.034g) and 2-dicyclohexylphosphino-2'-(N,N-dimethylamino)biphenyl (0.091g) were added to degassed dioxane (4ml). After 15 min 1-cyclobutyl-4-(4-piperidinyloxy)piperidine (D6) (0.150g) and sodium *tert*-butoxide (0.095g) were added and the reaction mixture heated at 100°C for 3h, then stirred at rt for 16h. Argonaught MP-NCO resin (0.4g) was added and the mixture allowed to stir for 1h. After diluting with MeOH (5ml) the crude mixture was passed through an SCX cartridge [10g, MeOH (80ml) then 2N NH_3 in MeOH (80ml)]. Chromatography [silica gel, eluting with (10%NH_3 in MeOH)/DCM, 0-10%] and treatment of the free base product dissolved in DCM (5ml) with HCl (1ml, 1M in diethyl ether), followed by evaporation afforded the title compound (E49) (0.10g). MS electrospray (+ion) 384 (MH^+). ^1H NMR δ (DMSO-d6): 10.75 (1H, s), 8.43 (1H, m), 7.62 (1H, d, J=8.8Hz), 7.44 (1H, d, 9.2Hz), 4.32-3.44 (5H, m, plus HOD), 3.35-3.06 (4H, m), 2.88-2.62 (2H, m), 2.42-1.40 (14H, m).

Abbreviations

DCM	dichloromethane
DMSO	dimethylsulfoxide
h	hour
min	minutes
rt	room temperature
TFA	trifluoroacetic acid
HOBt	1-hydroxybenzotriazole
EDC	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride

All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

Biological Data

A membrane preparation containing histamine H3 receptors may be prepared in accordance with the following procedures:

(i) Generation of histamine H3 cell line

DNA encoding the human histamine H3 gene (Huvar, A. *et al.* (1999) Mol. Pharmacol. **55(6)**, 1101-1107) was cloned into a holding vector, pCDNA3.1 TOPO (InVitrogen) and its cDNA was isolated from this vector by restriction digestion of plasmid DNA with the enzymes BamH1 and Not-1 and ligated into the inducible expression vector pGene (InVitrogen) digested with the same enzymes. The GeneSwitch™ system (a system where in transgene expression is switched off in the absence of an inducer and switched

on in the presence of an inducer) was performed as described in US Patent nos: 5,364,791; 5,874,534; and 5,935,934. Ligated DNA was transformed into competent DH5α E. coli host bacterial cells and plated onto Luria Broth (LB) agar containing Zeocin™ (an antibiotic which allows the selection of cells expressing the sh ble gene which is present on pGene and pSwitch) at 50μg ml^{-1}. Colonies containing the re-ligated plasmid were identified by restriction analysis. DNA for transfection into mammalian cells was prepared from 250ml cultures of the host bacterium containing the pGeneH3 plasmid and isolated using a DNA preparation kit (Qiagen Midi-Prep) as per manufacturers guidelines (Qiagen).

CHO K1 cells previously transfected with the pSwitch regulatory plasmid (InVitrogen) were seeded at 2x10e6 cells per T75 flask in Complete Medium, containing Hams F12 (GIBCOBRL, Life Technologies) medium supplemented with 10% v/v dialysed foetal bovine serum, L-glutamine, and hygromycin (100μg ml^{-1}), 24 hours prior to use. Plasmid DNA was transfected into the cells using Lipofectamine plus according to the manufacturers guidelines (InVitrogen). 48 hours post transfection cells were placed into complete medium supplemented with 500μg ml^{-1} Zeocin™.

10-14 days post selection 10nM Mifepristone (InVitrogen), was added to the culture medium to induce the expression of the receptor. 18 hours post induction cells were detached from the flask using ethylenediamine tetra-acetic acid (EDTA; 1:5000; InVitrogen), following several washes with phosphate buffered saline pH 7.4 and resuspended in Sorting Medium containing Minimum Essential Medium (MEM), without phenol red, and supplemented with Earles salts and 3% Foetal Clone II (Hyclone). Approximately 1x 10e7 cells were examined for receptor expression by staining with a rabbit polyclonal antibody, 4a, raised against the N-terminal domain of the histamine H3 receptor, incubated on ice for 60 minutes, followed by two washes in sorting medium. Receptor bound antibody was detected by incubation of the cells for 60 minutes on ice with a goat anti rabbit antibody, conjugated with Alexa 488 fluorescence marker (Molecular Probes). Following two further washes with Sorting Medium, cells were filtered through a 50μm Filcon™ (BD Biosciences) and then analysed on a FACS Vantage SE Flow Cytometer fitted with an Automatic Cell Deposition Unit. Control cells were non-induced cells treated in a similar manner. Positively stained cells were sorted as single cells into 96-well plates, containing Complete Medium containing 500μg ml^{-1} Zeocin™ and allowed to expand before reanalysis for receptor expression via antibody and ligand binding studies. One clone, 3H3, was selected for membrane preparation.

(ii) Membrane preparation from cultured cells

All steps of the protocol are carried out at 4°C and with pre-cooled reagents. The cell pellet is resuspended in 10 volumes of buffer A2 containing 50mM N-2-hydroxyethylpiperazine-N'-2-ethanesulfonic acid (HEPES) (pH 7.40) supplemented with 10e-4M leupeptin (acetyl-leucyl-leucyl-arginal; Sigma L2884), 25μg/ml bacitracin (Sigma B0125), 1mM ethylenediamine tetra-acetic acid (EDTA), 1mM phenylmethylsulfonyl fluoride (PMSF) and 2x10e-6M pepstain A (Sigma). The cells are then homogenised by

2 x 15 second bursts in a 1 litre glass Waring blender, followed by centrifugation at 500g for 20 minutes. The supernatant is then spun at 48,000g for 30 minutes. The pellet is resuspended in 4 volumes of buffer A2 by vortexing for 5 seconds, followed by homogenisation in a Dounce homogeniser (10-15 strokes). At this point the preparation is aliquoted into polypropylene tubes and stored at -70°C.

Compounds of the invention may be tested for in vitro biological activity in accordance with the following assays:

(I) Histamine H3 binding assay

For each compound being assayed, in a white walled clear bottom 96 well plate, is added:-

(a) 10μl of test compound (or 10μl of iodophenpropit (a known histamine H3 antagonist) at a final concentration of 10mM) diluted to the required concentration in 10% DMSO;

(b) 10μl ^{125}I 4-[3-(4-iodophenylmethoxy)propyl]-1H-imidazolium (iodoproxyfan) (Amersham; 1.85MBq/μl or 50μCi/ml; Specific Activity ~2000Ci/mmol) diluted to 200pM in assay buffer (50mM Tris(hydroxymethyl)aminomethane buffer (TRIS) pH 7.4, 0.5mM ethylenediamine tetra-acetic acid (EDTA)) to give 20pM final concentration; and

(c) 80μl bead/membrane mix prepared by suspending Scintillation Proximity Assay (SPA) bead type WGA-PVT at 100mg/ml in assay buffer followed by mixing with membrane (prepared in accordance with the methodology described above) and diluting in assay buffer to give a final volume of 80μl which contains 7.5μg protein and 0.25mg bead per well – mixture was pre-mixed at room temperature for 60 minutes on a roller.

The plate is shaken for 5 minutes and then allowed to stand at room temperature for 3-4 hours prior to reading in a Wallac Microbeta counter on a 1 minute normalised tritium count protocol. Data was analysed using a 4-parameter logistic equation.

(II) Histamine H3 functional antagonist assay

For each compound being assayed, in a white walled clear bottom 96 well plate, is added:-

(a) 10μl of test compound (or 10μl of guanosine 5'- triphosphate (GTP) (Sigma) as non-specific binding control) diluted to required concentration in assay buffer (20mM N-2-Hydroxyethylpiperazine-N'-2-ethanesulfonic acid (HEPES) + 100mM NaCl + 10mM $MgCl_2$, pH7.4 NaOH);

(b) 60μl bead/membrane/GDP mix prepared by suspending wheat germ agglutinin-polyvinyltoluene (WGA-PVT) scintillation proximity assay (SPA) beads at 100mg/ml in assay buffer followed by mixing with membrane (prepared in accordance with the methodology described above) and diluting in assay buffer to give a final volume of 60μl which contains 10μg protein and 0.5mg bead per well – mixture is pre-mixed at 4°C for 30 minutes on a roller and just prior to addition to the plate, 10μM final concentration of guanosine 5' diphosphate (GDP) (Sigma; diluted in assay buffer) is added;

The plate is incubated at room temperature to equilibrate antagonist with receptor/beads by shaking for 30 minutes followed by addition of:

(c) 10µl histamine (Tocris) at a final concentration of 0.3µM; and

(d) 20µl guanosine 5' [γ35-S] thiotriphosphate, triethylamine salt (Amersham; radioactivity concentration = 37kBq/µl or 1mCi/ml; Specific Activity 1160Ci/mmol) diluted to 1.9nM in assay buffer to give 0.38nM final.

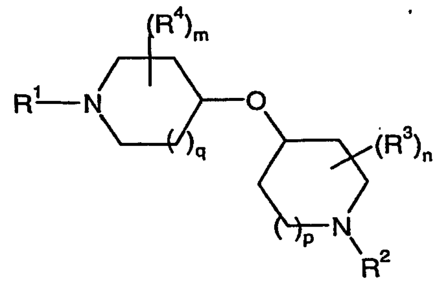
The plate is then incubated on a shaker at room temperature for 30 minutes followed by centrifugation for 5 minutes at 1500 rpm. The plate is read between 3 and 6 hours after completion of centrifuge run in a Wallac Microbeta counter on a 1 minute normalised tritium count protocol. Data is analysed using a 4-parameter logistic equation. Basal activity used as minimum i.e. histamine not added to well.

Results

The compounds of Examples E1-E49 were tested in the histamine H3 functional antagonist assay and exhibited pK_b values > 8.0. More particularly, the compounds of E2-E13, E15-E17 and E21-E49 exhibited pK_b values ≥ 9.0. Most particularly, the compounds of E17 and E38 exhibited pK_b values > 9.5.

CLAIMS

1. A compound of formula (I) or a pharmaceutically acceptable salt thereof:



(I)

wherein:
R^1 represents aryl, heteroaryl,-aryl-X-aryl, -aryl-X-heteroaryl, -aryl-X-heterocyclyl, -heteroaryl-X-heteroaryl, -heteroaryl-X-aryl or –heteroaryl-X-heterocyclyl;
wherein said aryl, heteroaryl and heterocyclyl groups of R^1 may be optionally substituted by one or more (eg. 1, 2 or 3) substituents which may be the same or different, and which are selected from the group consisting of halogen, hydroxy, cyano, nitro, oxo, haloC_{1-6} alkyl, polyhaloC_{1-6} alkyl, haloC_{1-6} alkoxy, polyhaloC_{1-6} alkoxy, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkoxyC_{1-6} alkyl, C_{3-7} cycloalkylC_{1-6} alkoxy, C_{1-6} alkanoyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylsulfonyl, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyloxy, C_{1-6} alkylsulfonylC_{1-6} alkyl, C_{1-6} alkylsulfonamidoC_{1-6} alkyl, C_{1-6} alkylamidoC_{1-6} alkyl, aryl, arylsulfonyl, arylsulfonyloxy, aryloxy, arylsulfonamido, arylcarboxamido, aroyl, or a group $NR^{15}R^{16}$, $-CONR^{15}R^{16}$, $-NR^{15}COR^{16}$, $-NR^{15}SO_2R^{16}$ or $-SO_2NR^{15}R^{16}$, wherein R^{15} and R^{16} independently represent hydrogen or C_{1-6} alkyl or together form a heterocyclic ring;
X represents a bond, O, CO, SO_2, OCH_2 or CH_2O;
R^2 represents C_{3-8} alkyl, C_{3-6} alkenyl, C_{3-6} alkynyl, C_{3-6} cycloalkyl, C_{5-6} cycloalkenyl or $-C_{1-4}$alkyl-C_{3-6} cycloalkyl;
wherein said C_{3-6} cycloalkyl groups of R^3 may be optionally substituted by one or more (eg. 1, 2 or 3) substituents which may be the same or different, and which are selected from the group consisting of halogen, C_{1-4} alkyl or trifluoromethyl groups;
each R^3 and R^4 group independently represents C_{1-4} alkyl;
m and n independently represents 0, 1 or 2;
p and q independently represents 1 or 2;
or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1 which is a compound of formula E1-E49 or a pharmaceutically acceptable salt thereof.

3. A compound according to claim 1 or claim 2 for use in therapy.

4. A compound according to claim 1 or claim 2 for use in the treatment of Alzheimer's disease.

5. A pharmaceutical composition which comprises a compound according to claim 1 or claim 2 and a pharmaceutically acceptable carrier or excipient.

PCT/EP2004/008061